

PCT

WORLD INTELLECTUAL PROPERTY
International Bur.



INTERNATIONAL APPLICATION PUBLISHED UNDER

WO 9607331A1

(51) International Patent Classification ⁶ :		A1	(11) International Publication Number:	WO 96/07331
A23L 1/09, C13F 3/00			(43) International Publication Date:	14 March 1996 (14.03.96)
(21) International Application Number:		PCT/FI95/00490		
(22) International Filing Date:		8 September 1995 (08.09.95)		
(30) Priority Data:		944182	9 September 1994 (09.09.94)	FI
(71) Applicant (for all designated States except US):		XYROFIN OY [FI/FI]; Kylliinkortti 2, FIN-00240 Helsinki (FI).		
(72) Inventors; and				
(75) Inventors/Applicants (for US only):		NURMI, Juha [FI/FI]; Vasarasepäntie 4 D 6, FIN-10330 Pinjainen (FI); HEIKKILÄ, Heikki [FI/FI]; Ristiniementie 32 G 33, FIN-02320 Espoo (FI); HALTTUNEN, Helena [FI/FI]; Huhtasuoenkatu 2-4 C 24, FIN-40320 Jyväskylä (FI); PERKKALAINEN, Paula [FI/FI]; Mustikkakuja 5-7 A 5, FIN-40340 Jyväskylä (FI); PITKÄNEN, Ilkka [FI/FI]; Kasälä 4 as. 6, FIN-40250 Jyväskylä (FI).		
(74) Agent:		OY KOLSTER AB; Iso Roobertinkatu 23, P.O. Box 148, FIN-00121 Helsinki (FI).		

(54) Title: COMPOSITION COMPRISING CO-CRYSTALS, METHOD FOR ITS MANUFACTURE, AND ITS USE

(57) Abstract

The invention relates to a dry composition comprising co-crystals. The co-crystals have been produced by grinding a mixture comprising at least two crystalline compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols in a solid state. The invention also relates to a method for producing such a composition. The composition may be used in the preparation of pharmaceutical products, sweets and chewing-gum, and in the food industry, for example in bakery products.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Larvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Composition comprising co-crystals, method for its manufacture, and its use

The present invention relates to compositions comprising co-crystals of at least two compounds, prepared by grinding. The compounds forming these co-crystals comprised in the composition of the invention are selected from a group consisting of monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols. The invention also relates to a method for producing such a composition, in which at least two crystalline compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols are ground as a mixture in a solid state at a temperature substantially lower than the melting points of the components.

Co-crystals are crystals formed by two or more compounds. A co-crystal has a unique crystal structure, which is different from the crystal structure of its components.

A physiologically acceptable polyol in this context means a hydrogenated product corresponding to a monosaccharide, disaccharide or oligosaccharide, i.e. a sugar alcohol.

Formation and characterization of co-crystals and their application to scientific research has been described in the doctoral dissertation of Gayle Marie Frankenbach, *The Preparation and Characterization of Hydrogen-Bonded Cocrystals with Applications to Materials Science*, 1989, University of Minnesota. The dissertation discloses as co-crystal producing methods co-crystallization from a solution, sublimation, and co-crystallization in a solid state, the last-mentioned being performed by grinding. The compounds from which co-crystals have been prepared in the study concerned

are substituted benzoic acid derivatives wherefrom co-crystals have been obtained both by crystallization from a solution and by grinding. In connection with the present invention, it has been unexpectedly found that co-crystals can be produced from sugars and sugar alcohols by grinding also in cases where crystallization from a solution will not produce co-crystals, but the compounds are separable in a pure form by crystallization from the solution.

Several particulate, i.e. powdery or granular, products having sugars and sugar alcohols as raw materials have been developed for the needs of the sweets and tabletting industries. Granular products in which the sugar or sugar alcohol is agglomerated with the aid of a binder and which are suitable for preparing tablets by the direct compression method are described for example in Finnish Patent 81 004 (xylitol with polyol as a binder), Finnish Patent Application 892797 (fructose with polyol as a binder) and Finnish Patent Application 932696 (xylitol with polymerized reducing sugar, alkali metal carboxymethyl cellulose or hydrogenated starch hydrolysate as a binder). In all these cases, the main component of the product is granulated by adding thereto an aqueous solution of a binder, and after granulation the product is dried and possibly sifted.

U.S. Patent 5 158 789 relates to a sorbitol/xylitol co-crystal produced by melt crystallization. In accordance with this patent, the co-crystal is produced by melting the starting materials into a homogeneous melt, cooling the melt with simultaneous stirring until a viscous mass has been obtained, and slowly cooling this mass until the sorbitol/xylitol mixture is crystallized throughout. The resultant co-crystal product is reported to be easier to tablet and to compound into chewing-gum, and also easier to handle in the sweets

industry and/or in pharmaceutical compositions, to make use of the advantageous effects of xylitol. The method for preparing co-crystals as disclosed in this patent publication is, however, expensive and slow and requires
5 high temperatures in the melting step. Furthermore, the crystallized solid mass must be crushed and possibly ground as a last step to make it usable. The product thus prepared by melting crystallization is an agglomerate in its physical properties. It is composed of
10 numerous microcrystals adhering together.

U.S. Patent 5 075 291 discloses a similar method for preparing a pharmaceutical composition, the composition comprising a crystalline sugar alcohol derived from at least one monosaccharide or polysaccharide and
15 having particles of at least one pharmaceutically active compound homogeneously dispersed in its crystal matrix.

The forming of a sorbitol/mannitol co-crystal by melt crystallization is disclosed in U.S. Patent 5 023 092. The product in accordance with this patent
20 comprises 5-35% by weight of mannitol. In this case, the starting materials are melted, stirred, the slightly cooled mass is extruded and allowed to cool for several days at room temperature and ground.

Finnish Patent Application 915876 relates to a
25 directly compressible powdery composition based on xylitol. Xylitol is stated to be present in an amount of at least 60% by weight of the composition, and possible other components of the composition include a saccharide, oligosaccharide or polysaccharide or a corresponding hydrogenated compound thereof. The process disclosed
30 comprises thermomechanical treatment in which the starting material mixture partly melts and is extruded. In accordance with the examples, the residence time in the heat zone is 5-300 seconds, and the extruded partly molten mass is cooled, crushed and sifted; the particle
35

size of the resultant product is in excess of 50 µm, typically in excess of 100 µm.

It is an object of the present invention to provide a composition comprising co-crystals formed by at least two compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols, which co-crystals can be prepared directly from solid starting materials without using solvents or high temperatures at which the risk of degradation of the materials being treated would exist. Simultaneously, time-consuming and energy-consuming heating and cooling steps are avoided. It is a further object of the present invention to provide a product comprising such co-crystals that is sufficiently fine without being subjected to any separate grinding step.

These objects are achieved with a substantially dry composition in accordance with the invention, which comprises co-crystals formed by at least two compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols, said co-crystals being produced by grinding a mixture of crystalline starting materials in a solid state.

The expression "substantially dry" in this context means that the amount of free water is less than about 5% by weight, preferably less than 1% by weight.

The invention also relates to a method for forming co-crystals from at least two compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols, the method being characterized in that a mixture of crystalline starting materials is ground in a solid state at a temperature substantially lower than the melting points of the components until a fine product consisting of co-crystals is produced.

The grinding temperature in the method of the

invention is not critical, as long as it is substantially lower than the melting point of any of the components in the mixture. For example, a grinding temperature suitable for a mixture of xylitol and sorbitol is 5 in the range 15-50 °C. As a rule, the grinding is preferably carried out at room temperature.

The invention is based on the finding that co-crystals can be obtained from compounds of the above type by grinding a mixture of starting materials in a 10 solid state, provided that the melting points of the starting materials are sufficiently close to one another. The difference between melting points should normally be less than about 30 °C, preferably less than 20 °C.

15 Monosaccharides, disaccharides and oligosaccharides that are possible in the preparation of the product of the invention include glucose, fructose, galactose, xylose, sucrose, mannose, lactose, maltose, isomaltose and raffinose. The physiologically acceptable polyol(s) 20 can be selected for instance from the following; sorbitol, xylitol, maltitol, lactitol, mannitol, galactitol and isomalt.

In a particularly preferred embodiment of the 25 invention, the co-crystals are formed of sorbitol and xylitol, in which case the product is also suitable for diabetics and the special advantages of xylitol are also gained for example in regard to caries prevention. Formation of a xylitol/sorbitol co-crystal by the method 30 of the invention is particularly unexpected for the reason that the generally employed method for purifying xylitol from sorbitol is to crystallize it from an aqueous solution containing these compounds, that is, such co-crystals are not formed from an aqueous solution. This completely deviates from what is to be anticipated 35 on the basis of the above dissertation by G. M. Franken-

bach.

In addition to the intended use of the product, the proximity of the melting points referred to above must be taken into account in the selection of the starting materials. Hence, grinding did not produce co-crystals from a mannitol/sorbitol mixture (difference between melting points about 65 °C) or from a mannitol/xylitol mixture (difference between melting points about 70 °C).

In the method of the invention, the grinding is carried out in a pulverizer wherein a large amount of energy is bound to the material to be ground and the particles are in intimate contact with one another for relatively long periods of time; the comminuting being based mainly on abrasion (rather than compression, impact or prall). Suitable grinding devices include rod mills, ball mills and tube mills.

The formation mechanism of co-crystals is considered to be - yet without being bound to this theory - such that as a result of the energy carried into the mixture in grinding, changes occur in the lattice structure of the crystalline starting materials, and when the difference in the melting points of the starting materials is small, the change in the lattice structure occurs nearly simultaneously in all of the crystalline starting materials. On account of rearrangement, co-crystals of the different components are produced. The fact that genuine co-crystals are involved, and not for instance a product formed by adherence of microcrystals of the different materials, has been ascertained with X-ray diffraction analyses (powder method) and differential scanning calorimetry (DSC), as will be explained in greater detail in the working example below.

In accordance with one embodiment, the composition of the invention comprises 5-100% of co-crystals.

The product obtained by grinding may also include pure starting materials. If, for example, a mixture of sorbitol and xylitol having 20 molar per cent of sorbitol and a balance of xylitol is ground, a product can be 5 obtained in which all sorbitol is co-crystallized with an amount of xylitol corresponding to the co-crystal form, and thus the product comprises both co-crystals and free xylitol.

Co-crystallization of xylitol and sorbitol will 10 take place at least at a molar ratio about 1:1, which in the above case will yield a product comprising 40% of co-crystals, the remainder being xylitol.

In accordance with the invention, a powdery co-crystallized product is directly obtained from the crystalline starting materials by grinding. In accordance 15 with one embodiment of the invention, the particle size of the product is below 50 µm. The product can be used as such for instance for tabletting and as a raw material for the sweets industry, or it may be agglomerated into 20 granules by methods known in the art, possibly employing binders as an aid in the agglomeration.

The scope of the present invention encompasses a product obtained by co-crystallization grinding and also 25 granules obtained therefrom by agglomeration, as well as the use thereof in the preparation of pharmaceutical products, sweets and chewing-gum, and in the food industry, for instance in bakery products.

The composition of the invention may also comprise additives incorporated into the starting material 30 mixture to be ground or into the product obtained from the grinding step or in connection with the agglomeration. Such additives may be e.g. aromas and dyes, polydextrose, inulin, carboxymethyl cellulose etc.

The invention will be illustrated in greater 35 detail in the following example.

Example

Sugar alcohol mixtures xylitol/D-sorbitol, xylitol/D-mannitol and D-mannitol/D-sorbitol were prepared by weighing these reagents into each mixture in given molar ratios. The reagents employed were: D-sorbitol, Fluka art. 85532, D-($-$)-mannitol, Merck art. 5982, and xylitol by Cultor Ltd, the purity of which was ascertained. The phases of the reagents and their thermal properties were measured prior to and after grinding by DSC and X-ray diffraction methods. The D-($-$)-mannitol by Merck was in the monoclinic δ -form, and the D-sorbitol by Fluka was a mixture of A and Γ -polymorphs.

The mixtures of crystalline reagents were ground in a ball mill pulverizer FRITSCH Pulverizette type 07.302 with a speed setting 8-9 (scale 1-10) for 20 minutes.

Thermogravimetric (TG), differential scanning calorimetric (DSC), and X-ray diffraction analyses were performed on each sample. The TG and DSC equipment was the following (PE = Perkin-Elmer, HP = Hewlett-Packard):

TG: PE TGA7, TAC7/DX, IBM PS/2 Model 55SX,
HP Plotter 7475A, PE TADS.TGS (software)
DSC: PE DSC-7, TAC7/PC, EPSON PC AX 2,
HP Plotter 7475A, PE DSC7 (software).

The TG analyses were performed in platinum crucibles in an air flow, flow rate 40-60 cm³/min. The samples weighed 3 to 9 mg, the heating rate was 2 °C/min, and the temperature range was 25-200 °C.

The DSC analyses were performed in 50 μ l perforated aluminium crucibles in nitrogen flow, flow rate 50-60 cm³/min. The samples weighed 3 to 9 g, the heating rate was 2 °C/min, and the temperature range was varied from the range 25-120 °C to the range 25-180 °C in accordance with the sample.

The X-ray diffraction patterns were measured with

the ENRAF NONIUS PDS120 diffractometer furnished with an INEL CPS120 detector. The radiation applied was monochromatic CuK α , radiation (wavelength 1.54056Å).

5 In accordance with the TG analyses, the samples did not contain any appreciable amounts of moisture. The "onset" and peak values for melting and the heats of fusion were measured from pure starting materials and ground pure starting materials by DSC. The mean values and their standard deviations from two analyses are shown in Table 1 (standard deviation values in parentheses). The polymorphic forms of the starting materials 10 were determined by DSC and X-ray diffraction.

15 The melting points of the starting materials employed ("onset", DSC) were as follows: xylitol 93.0 °C, D-sorbitol 97.0 °C and D-mannitol 164.4 °C.

20 The phase diagrams for the xylitol/D-mannitol, D-mannitol/D-sorbitol and xylitol/D-sorbitol systems were drawn up by using the melting peak values obtained from the DSC graphs, and they are shown in Figures 1, 2 and 3 in which

Figure 1 is a phase diagram for the system xylitol/D-mannitol,

25 Figure 2 is a phase diagram for the system D-mannitol/D-sorbitol, and

Figure 3 is a phase diagram for the system xylitol/D-sorbitol.

30 The horizontal line shown in Figure 3 is the mean value of the melting points of the xylitol/D-sorbitol co-crystals in the zone 0.25/0.75-0.75/0.25 of the molar ratios (xylitol/D-sorbitol) of the co-crystal.

A. Systems xylitol/D-mannitol and D-sorbitol/D-mannitol (comparison)

35 In accordance with the phase diagrams, xylitol/D-mannitol and D-sorbitol/D-mannitol showed no signs of co-crystal formation in the solid state. The melting

point for the sugar alcohol having the lower melting point (xylitol and D-sorbitol, respectively) changed only very little when a sugar alcohol having a higher melting point (D-mannitol) was present. The melting 5 point of D-mannitol decreased when the molar ratio of xylitol or D-sorbitol, respectively, increased, in which situation xylitol and D-sorbitol were present as impurities in D-mannitol. The total heats of fusion of the melting process as measured for these samples were equivalent to the values calculated from the heats of fusion 10 of pure samples when the molar ratios of the samples were taken into account. The DSC graphs determined for samples in which the starting materials had been separately ground and thereafter mixed were equivalent to the 15 DSC graphs for samples in which the starting materials had been ground together.

B. System xylitol/D-sorbitol (in accordance with invention)

The phase diagram for the xylitol/D-sorbitol system differed from the phase diagrams of the two previous 20 systems. It complied with the shape of the phase diagrams of two such components as do not form solid solutions with one another. However, the DSC patterns showed no characteristic configuration of eutectic melting, 25 which would have been perceived as a sharp melting peak in the DSC graph. The DSC graphs that were measured from samples in which the starting materials had been separately ground and thereafter mixed differed from the DSC curves of samples in which the starting materials had 30 been ground together.

Figure 4 shows the normalized DSC curves of xylitol/sorbitol mixtures for a case where the starting materials have been ground separately and for a case where they have been ground together.

35 In the phase diagram for the xylitol/D-sorbitol

system (Figure 3), the intersection of the two lines gives 76.2 °C as the melting point for the co-crystal of these compounds and 0.495/0.505 as the molar ratio (xylitol/D-sorbitol) thereof. The mean value and standard deviation for the melting peak values calculated for molar ratios 0.25/0.75 and 0.75/0.25 was 76.1 (0.3) °C. A small slope can be seen in the molar ratio range 0.8/0.2-0.95/0.05 (xylitol/D-sorbitol) in Figure 3. In this molar ratio range, also the melting point of the co-crystal changes. It is possible that there is also another co-crystal that is formed in this range.

The analysis results clearly show that the samples obtained by grinding together xylitol and D-sorbitol in a ball mill pulverizer for 20 minutes contained a co-crystal product. The X-ray diffraction analyses confirmed that these samples contained a new product along with the pure starting materials. The presence of this product can be seen as an additional peak in Figure 5 which shows X-ray diffraction patterns for xylitol, D-sorbitol and a product prepared from these compounds that contains a co-crystal.

The effect of the grinding time on a sample containing xylitol and D-sorbitol in a molar ratio 1:1 was also studied. It was found that the melting peak for the co-crystal in the DSC graphs became sharper when the grinding time was increased, which indicated an increase in co-crystallized material. The whole heat of fusion was decreased with increasing grinding time: with 20 minutes grinding time, the whole heat of fusion was 29.8 kJ/mol and with 60 minutes grinding time 27.7 kJ/mol.

Table 1
Mean values for starting material melting "onset" and peak values and heats of fusion (ΔH).
Standard deviations of mean values in parentheses.

Name and molec. formula	M	"onset"	peak	ΔH	Literature values			
	g/mol	°C	°C	kJ/mol	"onset"	peak	m.p. °C	ΔH kJ/mol
<chem>C6H12O5</chem>	152.1	93.0(0.5)	94.3(0.6)	36.4(0.3)	90	100	93-94	38.0 [1]
		(cryst.)	(cryst.)	(cryst.)			92-94	[2]
<chem>C6H14O6</chem>	182.2	97.0(0.08)	98.6(0.07)	31.1(0.3)			85	[3]
		(cryst.)	(cryst.)	(cryst.)			92	[3]
<chem>C6H14O6</chem>	182.2	164.4(1.0)	166.2(0.9)	49.8(1.0)	165.4	167.1	(6-phase)	50.8 [4]
		(cryst.)	(cryst.)	(cryst.)				
<chem>C6H14O6</chem>	162.7(0.6)	165.2(0.6)	162.7(0.6)	49.2(0.09)				
		(ground)	(ground)	(ground)				

References: [1] A. Reamy and F. Schweizer, J. Thermal Anal., Vol. 28 (1983) 95.

[2] H. S. Kim and G. A. Jeffrey, Acta Cryst. B25 (1969) 2607.

[3] Y. J. Park, G. A. Jeffrey and W. C. Hamilton, Acta Cryst. B27 (1971) 2393.

[4] I. Pitkänen, P. Perkkalainen and H. Reutilainen, Thermochim. Acta, 214 (1993) 157.

Claims:

1. A substantially dry composition comprising co-crystals, characterized in that the co-crystals have been prepared by grinding a mixture comprising at least two crystalline compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols in a solid state, the difference between the melting points of said compounds being less than about 30°C.
5
2. A composition as claimed in claim 1, characterized in that the difference between the melting points is less than 20°C.
10
3. A composition as claimed in claim 1 or claim 2, characterized in that the co-crystals comprise two polyols.
15
4. A composition as claimed in claim 3, characterized in that the polyols are xylitol and sorbitol.
5. A composition as claimed in claim 4, characterized in that the molar ratio of xylitol and sorbitol in the composition is from 9:1 to 1:9.
20
6. A composition as claimed in claim 5, characterized in that the molar ratio of xylitol and sorbitol in the co-crystals is about 1:1.
25
7. A composition as claimed in claim 6, characterized in that the co-crystals have a melting point in the range 70-80°C as determined by DSC (differential scanning calorimetry).
8. A composition as claimed in claim 6, characterized in that the co-crystals have an X-ray diffraction pattern essentially as shown in Figure 5 by the uppermost curve.
30
9. A composition as claimed in any one of the preceding claims, characterized in that
35

the amount of co-crystals contained therein is 5-100% by weight of the composition.

10. A method for producing a substantially dry composition comprising co-crystals, characterized by grinding a mixture comprising at least two crystalline compounds selected from monosaccharides, disaccharides and oligosaccharides and physiologically acceptable polyols in a solid state until a fine product consisting of co-crystals is produced.

11. A method as claimed in claim 10, characterized in that the grinding temperature is substantially lower than the melting points of the components of the mixture.

12. A method as claimed in claim 10 or claim 11, characterized in that said two compounds are xylitol and sorbitol.

13. A method as claimed in claim 12, characterized in that the grinding is carried out at a temperature of 15-50°C.

14. A method as claimed in any one of claims 10-13, characterized in that the grinding is carried out by a ball mill.

15. A method as claimed in any one of claims 10-14, characterized in that it further comprises a step in which the product prepared by grinding is agglomerated into granules.

16. A method as claimed in any one of claims 10-15, characterized in that additives not involved in the co-crystallization are added to the mixture to be treated prior to grinding, after grinding or in connection with agglomeration.

1 / 5

Figure 1

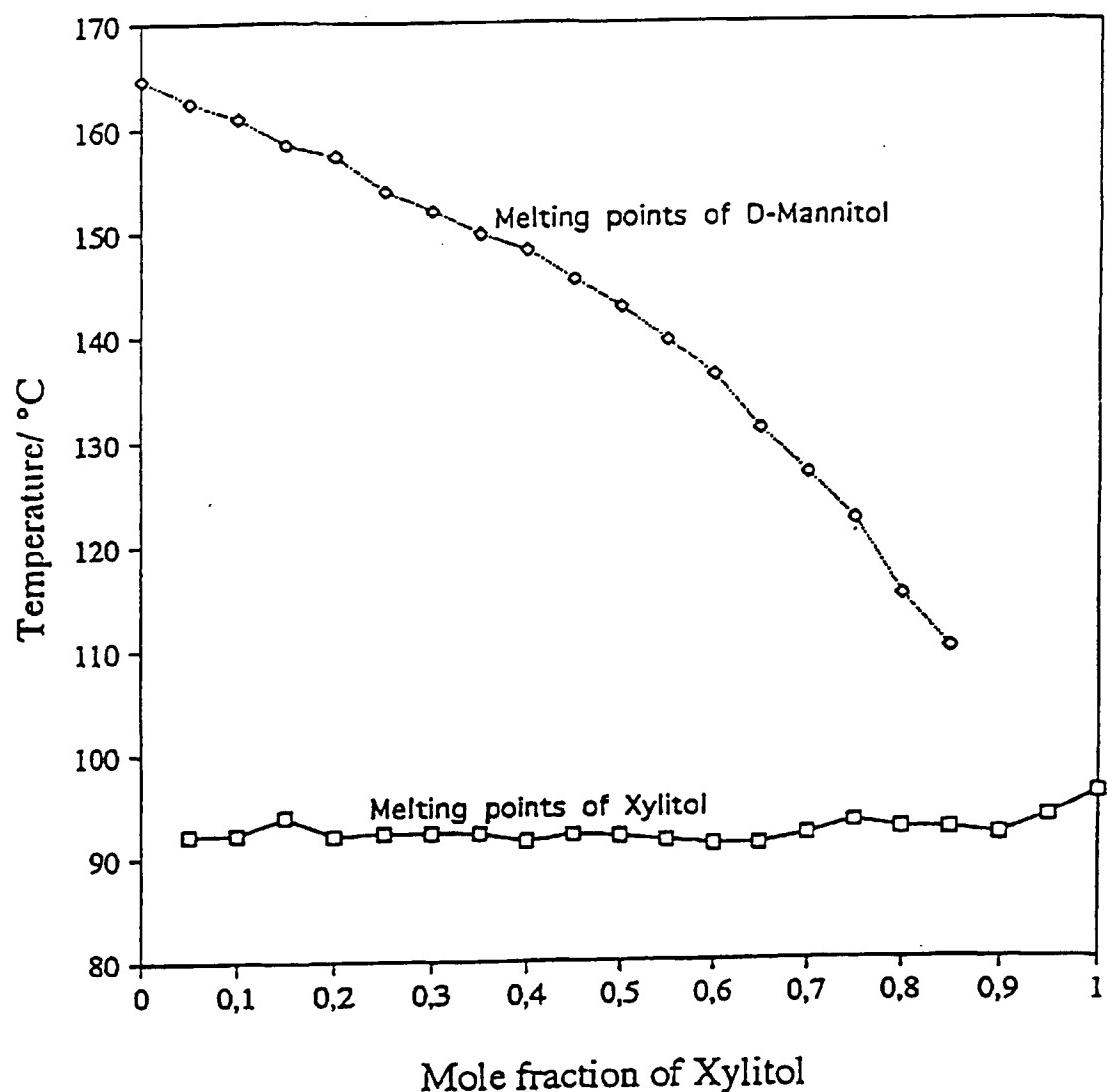
**SUBSTITUTE SHEET**

Figure 2

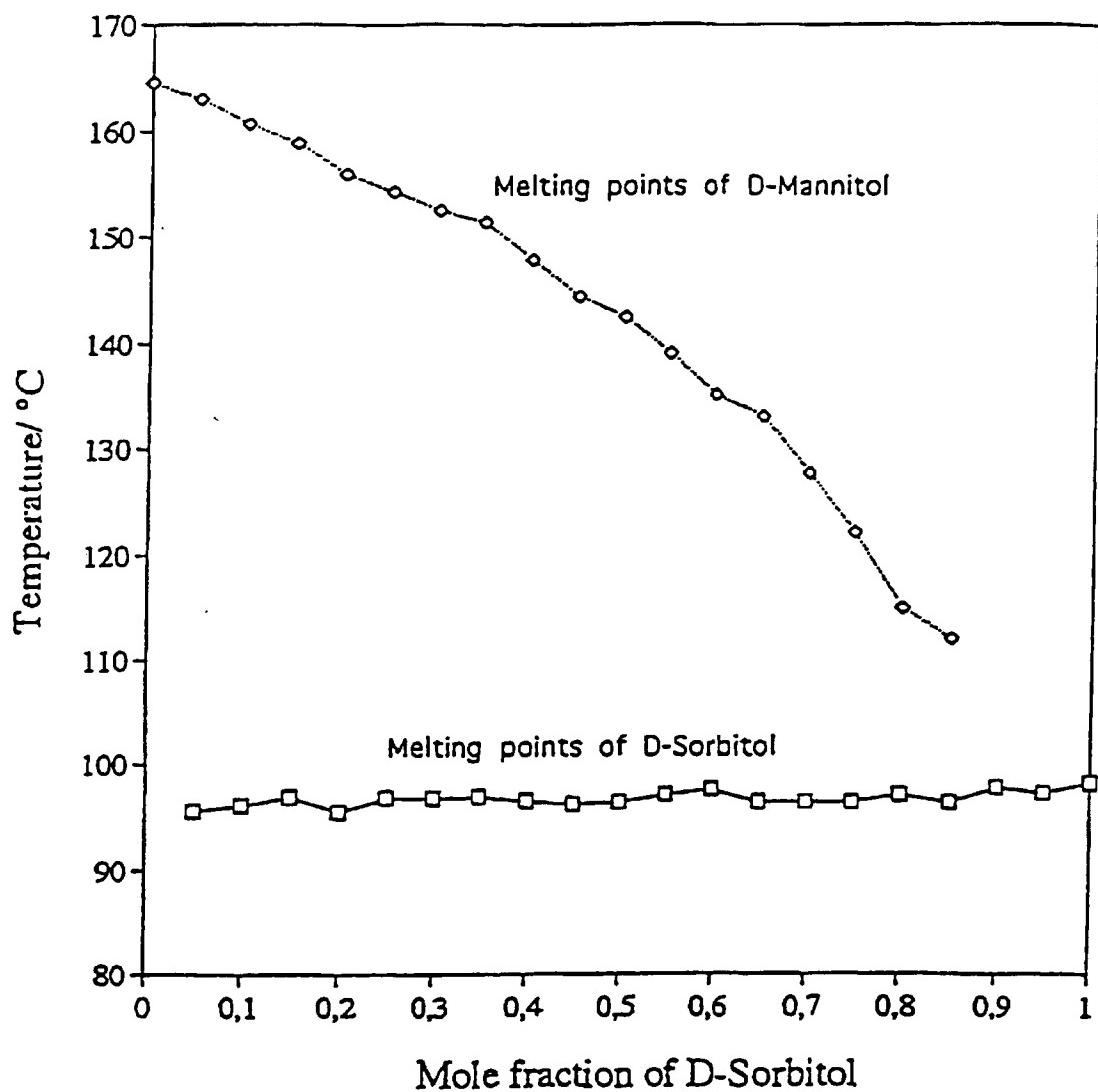
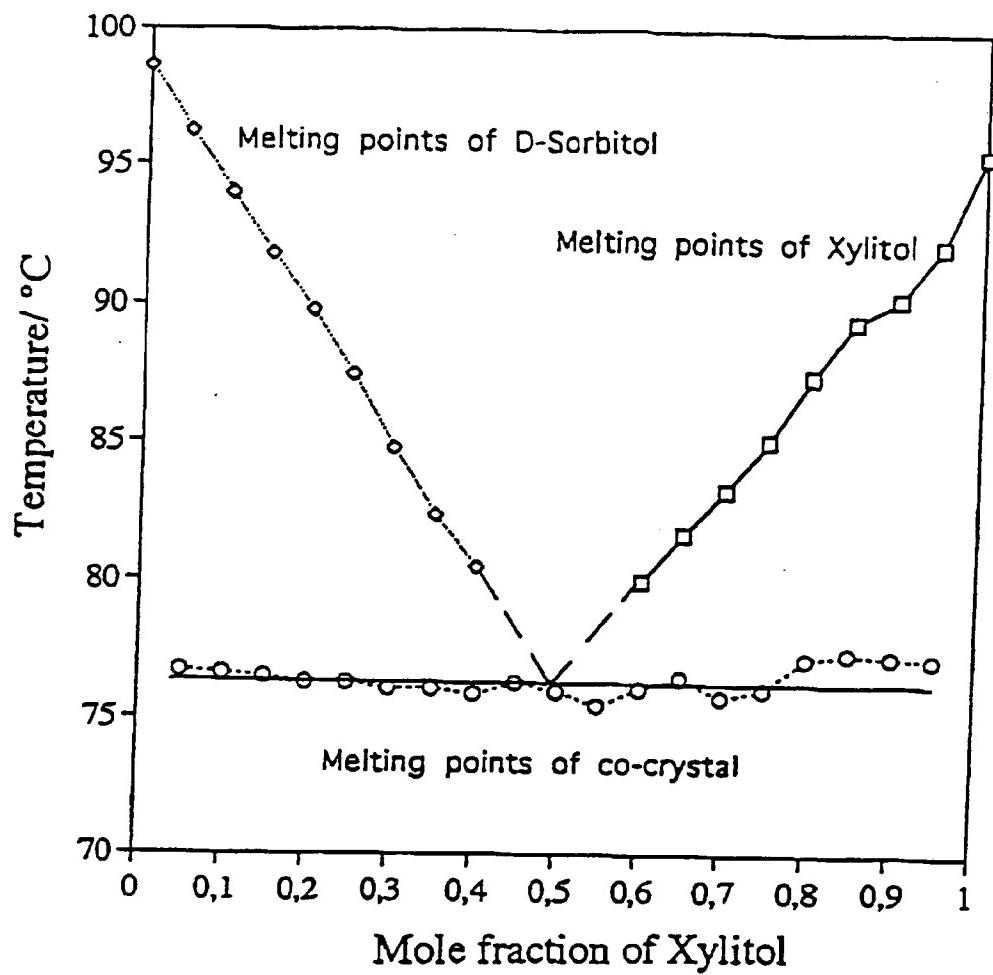
**SUBSTITUTE SHEET**

Figure 3



4/5

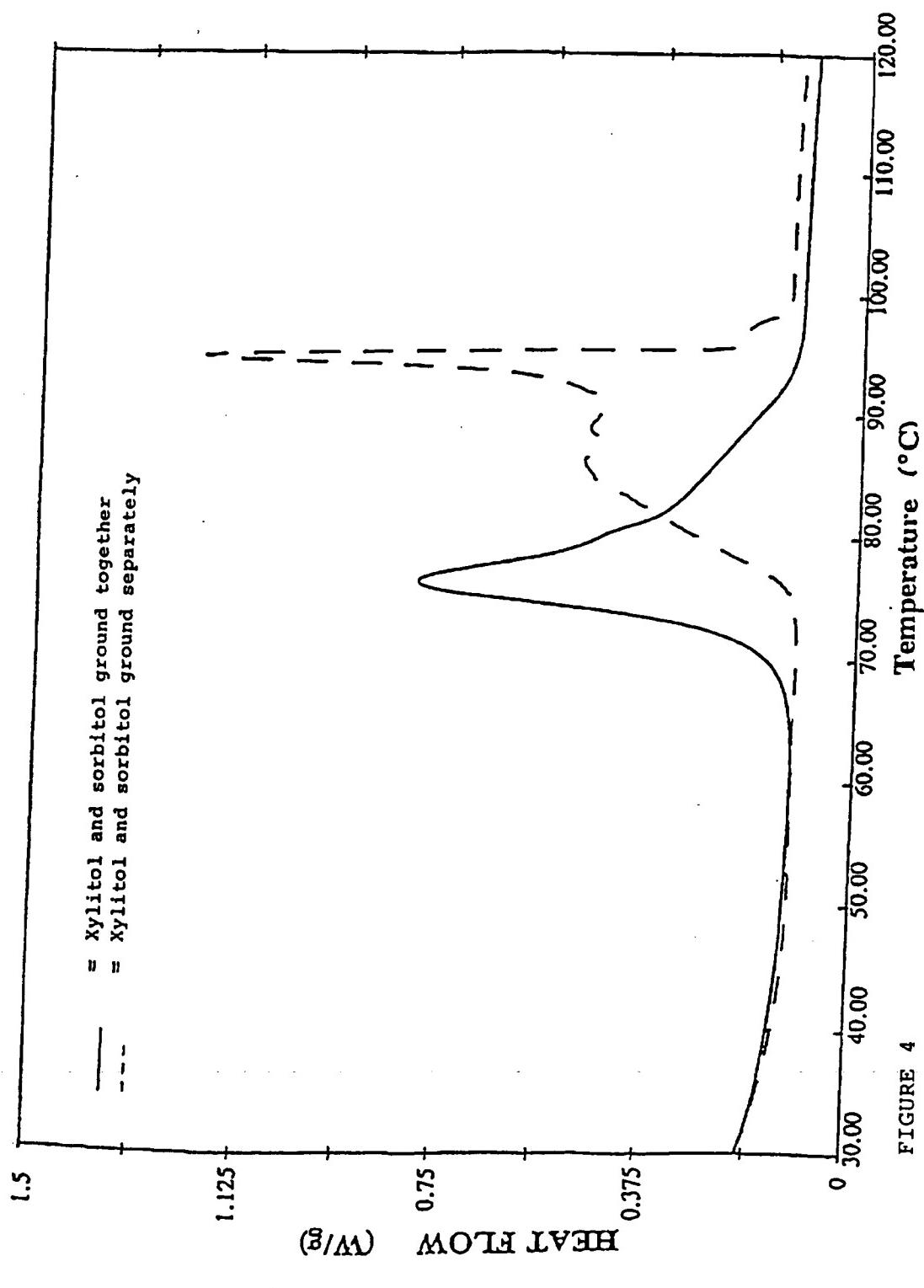


FIGURE 4

SUBSTITUTE SHEET

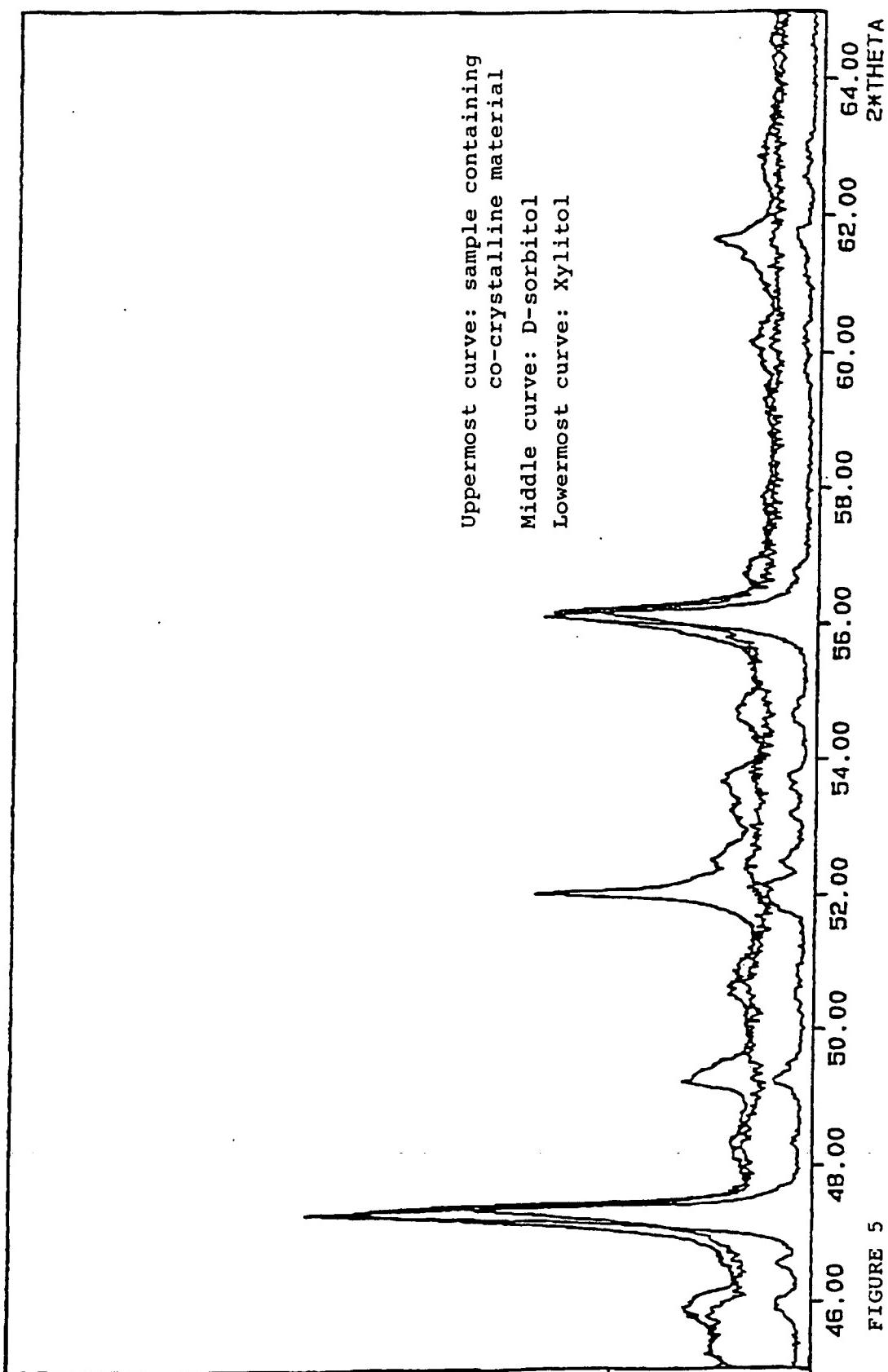


FIGURE 5

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 95/00490

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A23L 1/09, C13F 3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C13F, C30B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS, WPI, CLAIMS, DIALINDEX(FOODSCI)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9421827 A1 (SUCROS OY), 29 Sept 1994 (29.09.94), page 4, line 30 - page 5, line 3 --	1-4,9,10-12
X	EP 0528604 A1 (ICI AMERICAS INC.), 24 February 1993 (24.02.93), claims 1,3-4, abstract -----	1-6

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

8 December 1995**02 -01- 1996**

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer
Agneta Österman Wallin
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/FI 95/00490

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9421827	29/09/94	NONE	
EP-A1- 0528604	24/02/93	AU-B- 660179	15/06/95
		AU-A- 2082792	11/02/93
		JP-A- 5201899	10/08/93
		US-A- 5158789	27/10/92